CHAPTER - I

INTRODUCTION

Research programs for the discovery of new drugs and for improving the evolution criteria is under exclusive investigation. In addition to this, knowledge of specific constituents of the mycobacterium cell and their biochemical roles has become advanced considerably in the recent years and may permit a more rational approach to new drug design for specific targets. Also recent improvements in understanding the mechanism of drug action and its resistance to them may be used as a route for designing new and better weapons to fight against the mycobacterial diseases.

Heterocyclic compounds have great applicability in pharmaceutics as they have specific chemical reactivity and provide false synthons in biosynthetic process as they block the normal functioning of biological receptors. The inhibition of amide resonance resulting in more susceptibility of β-lectum to nucleophile is considered at least in part responsible for antibacterial property, apparently by acetylating transpeptidase and thus inhibiting bacterial cell wall biosynthesis.

Heterocyclic compounds containing nitrogen and sulfur atoms are of vital importance due to their variable biological activities and considerable diversity in the heterocyclic ring system[1].

Fused pyrimidines such as purines, pteridines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines, and pyrrolopyrimidines continue to attract considerable attention because of their great practical usefulness, primarily, due to a wide spectrum of biological activities. Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annulated five-member heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of chemistry and biology of isomeric thienopyrimidines have been reviewed[2].

Thienopyrimidine derivatives are characterized by a very broad spectrum of biological activities, which includes several dozen of activities.

Some thienopyrimidine derivatives exhibit antiallergic[3], antiatherosclerotic[4], antibacterial[5], antitumor[6], antiviral[7], antihypertensive[8], antidepressant[9], antidiabetic[10], antihistaminic[11], antimicrobial[12], spasmolytic[13], analgesic[14], antiinflammatory[15] and neurotropic[16] activities.

Many thieno[2,3-*d*]pyrimidine derivatives were patented as phosphodiesterase inhibitors[17] and various receptor antagonists[18]. Various thieno[2,3-*d*]pyrimidine and thieno[3,2-*d*]pyrimidine derivatives show pronounced radioprotective[19], act as immunomodulators[20] and compounds used for prophylaxis and therapy of cerebral ischemia[21], malaria[22], tuberculosis[23], Alzheimer's disease[24] and Parkinson's disease[25]. Novel classes of thienopyrimidines have been identified as potent inhibitors of VEGFR-2 kinase[26], ErbB kinase[27] and p38 kinase[28].

Problems of biological activity of isomeric thienopyrimidines were also touched on in patents and publications. In addition, promising pesticides fungicides, herbicides[29] and insecticides[30] were found among these derivatives. On other aspects, practical use of 4-[4-(arylazo)phenoxy]-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-*d*]pyrimidines as disperse dyes[31] and 2,4-dimethyl thio-6-phenylthieno[3,2-*d*] pyrimidine as a material for nonlinear optics is well documented.

Chalcones are a class of privileged structures that have a wide range of biological properties[32]. An area of particular interest is their potential as anticancer agent[33]. For which several modes of action have been proposed, several oxygenated chalcones and bischalcone are reported as antimalarial agents[34]. Also literature survey revealed that amino chalcones and corresponding bi-heterocyclics derived from furan enhanced biological activity[35].

Schiff base can be synthesized by the acid catalyzed reaction of amines and ketones or aldehydes since it was discovered by Schiff imines are known as Schiff base. A large number of Schiff base possess various pharmacological activities such as anticancer and antimicrobial[36].

Thiazolidinones and Azetidinones are other important pharmacodynamic heterocyclic nucleus which when incorporated in different heterocyclic templates have been reported to possess potent anti-inflammatory activity, analgesic, antifungal[37], antibacterial[38], antipsychotic, antiviral, antitubercular, anticancer and anti-HIV activity[39].

In the light of the above observation, we have synthesized a new series of thieno[2,3-*d*]pyrimidine derivatives by incorporating the Benzothiazole, Chalcone, Acid-amide, Schiff base, Azetidinone, and Thiazolidinone moieties.

Synthetic approaches to the construction of thienopyrimidines are sufficiently well developed. Three possible types of annulations of thiophene to the pyrimidine ring correspondingly, three isomeric thienopyrimidines are well known: thieno[2,3-*d*]pyrimidine, thieno[3,2-*d*]pyrimidine and thieno[3,4-*c*] pyrimidine. The present work will be related to the synthesis of thieno[2,3-*d*]pyrimidine compounds.

CHAPTER - II

EXPERIMENTAL

SERIES-I: *N*-(Substituted benzo[*d*]thiazol-2-yl)-5,6-dimethylthieno[2,3-*d*] pyrimidin-4-amine

The title compounds were obtained by the initial cyclization of 2-amino-4,5-dimethylthiophene-3-carboxylate with formamide then chlorination and followed by the condensation with substituted 2-amino benzothiazole in basic medium.

SERIES-II: 3-(substituted phenyl)-1-(4-(5,6-dimethylthieno[2,3-*d*] pyrimidin-4-ylamino)phenyl)prop-2-en-1-one

The title compounds were obtained by the initial cyclization of 2-amino-4,5-dimethylthiophene-3-carboxylate with formamide then chlorination and followed by the condensation with *p*-amino acetophenone was further treated with different substituted benzaldehydes in basic medium.

SERIES-III: *N*-(5,6-dimethyl-2-(methylthio)-4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl) substituted benzamide

The title compounds were obtained by the initial cyclization of 2-amino-4,5-dimethylthiophene-3-carboxylate with carbon disulphide and hydrazine hydrate in basic medium followed by methylation which on treatment with different substituted benzoyl chlorides.

SERIES-IV: 2-(3-chloro-2-oxo-4-(substituted phenyl) azetidin-1-ylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one

The title compounds were obtained by the initial cyclization of 2-amino-4,5-dimethylthiophene-3-carboxylate with potassium thiocyanate and on treatment with hydrazine hydrate followed by the reaction with different substituted benzaldehydes which on cyclization with chloro acetyl chloride.

SERIES-V: 5,6-dimethyl-2-(4-oxo-2(substituted phenyl) thiazolidin-3-yl-amino) thieno[2,3-*d*]pyrimidin-4(3*H*)-one

The title compounds were obtained by the initial cyclization of 2-amino-4,5-dimethylthiophene-3-carboxylate with potassium thiocyanate and on treatment with hydrazine hydrate followed by the reaction with different substituted benzaldehydes which on cyclization with thioglycolic acid and anhydrous $ZnCl_2$.

SERIES-VI: 2-(2-(substituted benzylidene) hydrazinyl)-5,6-dimethyl-*N*-(4-nitrophenyl)thieno[2,3-*d*]pyrimidin-4-amine

The title compounds were obtained by the initial cyclization of 2-amino-4,5-dimethylthiophene-3-carboxylate with potassium thiocyanate and on treatment with hydrazine hydrate followed by chlorination and condensation with *p*-nitroaniline which on further reaction with different substituted benzaldehydes in acidic medium.

SERIES-VII: 3-(5,6-dimethyl-4-(4-nitrophenylamino)thieno [2,3-*d*] pyrimidin-2-ylamino)-2-(substituted phenyl)thiazolidin-4-one

The title compounds were obtained by cyclization of 2-(2-(substituted benzylidene) hydrazinyl)-5,6-dimethyl-*N*-(4-nitrophenyl)thieno[2,3-*d*]pyrimidin-4-amine with thioglycolic acid and anhydrous $ZnCl_2$.

CHAPTER - III

CHARACTERIZATION

All the heterocyclic compounds of each series were characterized by thin layer chromatography, elemental analysis, infrared spectroscopy and some representatives by nuclear magnetic resonance spectroscopy.

CHAPTER - IV

BIOLOGICAL EVALUATION

All the synthesized compounds have been evaluated for their *in vitro* biological assay (antimicrobial activity) towards gram positive and gram negative microbial strains. The biological activities of the synthesized compounds have been compared with standard drugs.

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